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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61D 19/00, A61F 6/08, A61M 31/00

A1

(11) International Publication Number: WO 98/33452

(43) International Publication Date: 6 August 1998 (06.08.98)

(21) International Application Number: PCT/NZ98/00011

(22) International Filing Date: 2 February 1998 (02.02.98)

(30) Priority Data:

314175	3 February 1997 (03.02.97)	NZ
314572	10 April 1997 (10.04.97)	NZ

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

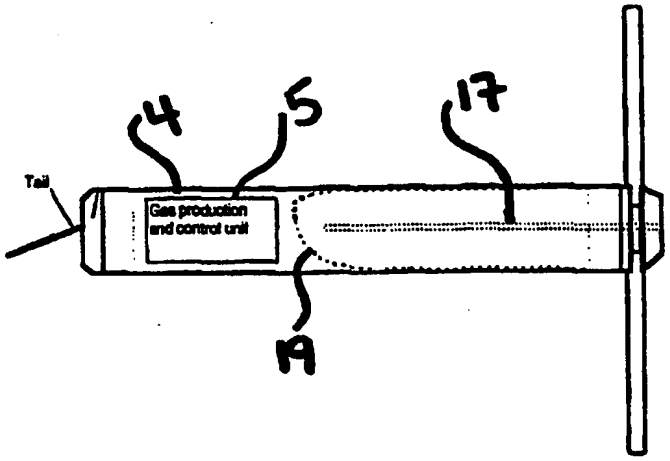
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ACTIVE DELIVERY DEVICE AND RELATED PROCEDURES

(57) Abstract

An intravaginal substance delivery device for achieving and maintaining a progesterone plasma level of 2 ng/ml for a period of at least 4 days, comprising an elongated body with a plurality of resilient radially–extending arms, said body further comprising a bladder (19) containing said substance whereupon the bladder (19) is compressed to expel said substance by the pressure of a gas created by passing an electric current through a hydrogel.



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"ACTIVE DELIVERY DEVICE AND RELATED PROCEDURES"

TECHNICAL FIELD

The present invention relates to active delivery device and related procedures. In one aspect the invention relates to active delivery devices locatable in a body cavity of an animal to actively release a substance (eg. useful by intra-vagina insertion of synchronising the oestrus of animals).

The related procedures include the prospect of optimising a delivery profile for an animal or species of animal utilising the flexibility in active delivery arising from the use of such an active delivery device and thereafter profiling a less active or passive delivery device to delivery to that optimised profile.

When one considers the mating of animals, it is useful for farmers to synchronise the oestrus of animals whether they be cattle beasts (whether for dairy or beef purposes) sheep, goats, horses, or the like where artificial insemination is practised. By way of example, in relation to cattle beasts, in a normal 365 day year 282 days on average is taken up of the year with the gestation period itself. With approximately 30 days to recover after delivery of its progeny each cow therefore has an average of only two and a half cycles if there is to be a timely management of the herd. Thus it is important over that remaining period of less than 53 days to ensure each cow in a herd becomes pregnant.

The traditional method of mating dairy cows with bulls is now largely superseded by the use of artificial insemination procedures which offers the prospect of rapid herd improvements although bulls are still presented to the herd frequently to catch those animals that have not conceived by the artificial insemination procedure should they comes into oestrus within a designated time.

There is therefore a great advantage attached to bringing such herd animals into oestrus simultaneously so as to make it easier to ensure effective usage of the artificial insemination procedure and subsequently to enable still within the "window" a further prospect of artificial insemination of those animals synchronistically brought to oestrus that have not already conceived.

Various means of achieving such a management of the synchronisation of the coming into oestrus of cows (whether heifers or lactating cows) and even sheep and goats has been disclosed in the art which includes the livestock improvement publication of this company (1995 edition) made available to interested parties by this company trading as INTERAG™ in respect of its intra vaginal Eazi-Breed™ CIDR® product line.

The disclosures in the aforementioned publication, the full contents of which are here included by way of reference, ensures to date the best procedure applicable at least to

New Zealand herds of cattle beasts to ensure a timely conception of a herd without a significant downgrading of the fecundity of the herd.

As used herein the term "synchronise" or the derivatives thereof in respect of the onset of oestrus of an animal is not restricted to exact synchrony but rather relates to a period of time usually measured in days over which the synchrony occurs.

Initial attempts using intra vaginal devices from which progesterone could be leached simply had the effect of preventing oestrus until after they were withdrawn thereby deriving some synchrony in the onset of oestrus thereafter during a period when a heifer or lactating cow is able to cycle this lead to a three day spread in the synchrony after a 12 to 15 day insertion of the intra vaginal progesterone containing device.

Subsequent efforts to confine the period of the synchrony lead to such a progesterone containing intra vaginal device being inserted shortly after, simultaneously with or shortly before the administration (usually intra vaginally) of an oestradiol. For instance the use of a CIDR® intra vaginal device as referred to the aforementioned publication simultaneously with a capsule containing ten milligrams of oestradiol and the retention of the CIDR® intra vaginal device in the animal for ten days led shortly thereafter to a three day synchrony onset of oestrus period.

More recently that last mentioned procedure has been refined for heifers to provide a two day period of synchrony with an 80% of the herd onset of oestrus within the first day. In this refined procedure at about day 6 of the 10 day insertion period a prostaglandin is injected.

The aforementioned procedures are now described in the art as are insemination procedures and the use of substantial repeats of the procedure within the available cycling period referred to so that there is at least one additional prospect of conception by artificial breeding within an appropriate economic window.

With all such procedures however the longer the period of the presence of the progesterone containing intra vaginal device in an animal (where about 15 days is the optimum for tightness of the synchronisation) there is a corresponding diminishment in the fertility of individual animals in the herd owing to the effect over time on the follicle development to the fertilisable egg stage. The use of the oestradiol changes follicle growth pattern. Hence with its use an optimisation of the fecundity prospects for the herd can be achieved by better balancing the tightness of the synchronisation (with longer insertion) against the loss of fertility (with longer insertion).

A cost factor arises in the adoption of such procedures as a farmer is faced with the costs of the intra vaginal progesterone containing device as well as the use of the oestradiol and/or prostaglandin materials additionally used. This ignores also the economic cost of

the artificial breeding materials themselves.

The intra vaginal progesterone containing devices hitherto used in New Zealand and to a large extent elsewhere are typified by the CIDR® product of this company depicted hereinafter in Figures 1 and 2 being a variable geometry device for vaginal insertion and retention which comprises a structural frame of a metal or appropriate plastics material (eg. nylon) encased in a progesterone impregnated plastics material (eg. silicone) from which the material can leach in the vaginal environment and from which it can be timely withdrawn by appropriate means (eg; a string, tail or a tool) to allow the animal to progress into oestrous shortly after the removal. Reference should be made to New Zealand Patent Specification No. 207341. Hereinafter the aforementioned device will be referred to by its registered trademark CIDR®.

The prior art CIDR™ devices of this company are intra vaginal passive delivery systems to be used in cattle for the control of oestrus. Two major uses are in the treatment of anoestrus and synchrony. Other uses include its role in embryo transfer and treatment of cystic ovaries.

Another product available in the market place of this kind is another variable geometry device and such a device is depicted hereinafter in Figure 3. Such a device is a helical coil capable of being helically tightened and which is retainable its helical form in the animals vagina. The device includes a withdrawal cord and carries a gelatine capsule which includes oestradiol so that there can be co-administration of the progesterone to be released over a protracted period and the oestradiol which is to be released at a different rate. Such a device includes a progesterone impregnated plastics matrix about a helical spine. Such a device is available from Sanofi Animal Health Limited, PO Box 209, Rhodes Way, Watford, Herts, WD2 4QE, England under its registered trademark PRID®.

Species specific enhancements to better ensure retention of devices abound. See for instance New Zealand Patent Specification No. 299060 that is relevant to pigs.

The aforementioned CIDR® and PRID® devices are manufactured in large volumes with the most expensive material being the progesterone active ingredient. Thus small reductions in the progesterone inclusion in such the devices will provide an economic advantage to a producer and to a farmer.

The CIDR® prior art device of this company has been marketed with a silicone plastics matrix about its spine which contains about 1.9 grams of progesterone (USP) which drops to 1.25 grams still retained in the silicone matrix if the device is withdrawn after only seven days in order to maximise fertility. The same device drops to 1.00 grams of progesterone if it is not withdrawn until after 15 days which is the optimum time for ensuring maximum synchrony.

The PRID® coil intra vaginal device contains at the outset 1.55 grams of progesterone which reduces down to 0.55 grams after 7 days and down to 0.86 grams after 15 days. The leach rate from the PRID® product may be affected in part by the inclusion of inorganic materials in the silicone plastics material such as calcium carbonate. The CIDR® silicone matrix for the progesterone is largely free of any such inclusions.

Our New Zealand Patent Specification No. 286492 discloses a passive delivery device of the CIDR™ type having advantages insofar as reducing the progesterone content is concerned but without any diminution of the delivery. In this respect please see Figure 4 which is a plot of the plasma progesterone levels for individual ovariectomised cows with this particular intra vaginal passive delivery device (CIDR-B™) against time. While the individual profiles of individual animals varies having regard to the nature of the animal, eg; its vaginal liquids etc. a general trend is evident, viz, a rapid release upon device insertion to rapidly elevate progesterone plasma levels above 2 ng/mL and to maintain a progesterone plasma level above 2 ng/mL until device removal whereupon the progesterone plasma level rapidly drops.

Therefore a programme of passive delivery utilising the CIDR-B™ with a silicone elastomer containing progesterone moulded over a T shape nylon spine and a CIDIROL™ capsule which contains oestradiol benzoate and is administered attached to the CIDR-B™ can act to ensure that a fresh follicle is present from the onset of progesterone delivery by the CIDR-B™ device. The length of insertion of the CIDR-B™ device varies but a period as short as five days can now be used. Within 24 - 48 hours after removal of the device the animal will enter oestrus thereby allowing the predetermined timing of insemination.

Active delivery devices have been used for the delivery of active ingredients into the bodies of mammals (whether for therapeutic purposes with a human or in order to achieve a therapeutic or some other advantageous effect in a non human mammal).

For example, PCT/US89/03705 (published as WO 90/02580) to Brown University Research Foundation discloses an implantable delivery system for biological factors. The disclosure envisages in some instances the use of a preprogrammed micro-processor to control a pumping system responsible, when activated, of actively delivering a desired therapeutic, biologically-active factor, (such as a drug) into the target region into which the implantable device has been inserted.

BACKGROUND ART

In September 1996 Plade Holdings Limited launched an active delivery device into the New Zealand market for delivery of active ingredients via the vaginal tract. The device was launched as the SMARTT1™ Intelligent Breeding Device. It included a micro-

processor chip programmed to deliver three different active ingredients - progesterone, oestradiol benzoate and clonprostenol sodium at various times and durations during a 12 day treatment program. Reference should be made to PCT/NZ96/00024 (published as WO 96/29025) of Advanced Animal Technology Limited which relates to the SMARTT1™ product at least in part.

In column 2 lines 52 to 26 WO90/02580 indicates, as an object, the provision of a compact infusion unit which is controlled by electric current supplied by batteries and regulated by means such as an electronic timer, biomedical control means or microprocessor control.

In the SMARTT1™ device each active ingredient is in a liquid form (dissolved in a suitable organic solvent) and is held in a drug reservoir. Each such reservoir is under positive pressure resulting from a spring acting on a plunger or piston. When a solenoid is activated a closure within the solenoid can be opened allowing the liquid to pass from the pressurised reservoir and through a channel running the length of the overall device to be released from its head. By far the bulk of the device (ignoring the variable geometry retention device aspects) are the controller and the pumping mechanisms which occupy greater than 50% of the volume of the device (circuit board, 2AAA batteries, wire, spring, seal, plunger and solid metal components) thus leaving (owing to vaginal tract insertion and retention considerations) the volume of the drug reservoir being limited to about 5 mL.

The present invention in one aspect recognises the desirability, as an alternative to the passive devices, of an active delivery device and in particular a device useful by way of intra-vaginal insertion of controlling the oestrus of animals. Such a device has the prospect of totally delivering its progesterone content.

US Patent 5,318,557 (Elan Medical Technologies Ltd) discloses "smart" pill constructions for insertion into a body cavity and having gas generating means to expand one chamber whilst by contraction of another expressing a substance via an outlet thereof. An electrolytic cell is disclosed as a preferred gas generator. Its New Zealand equivalent is No. 253782.

US Patent 5,354,264 of Insutech, Inc. discloses a drug delivery device which utilises gas pressure from free oxygen and hydrogen derived from the electrolysis of water at the electrodes in negatively charged polymeric hydogels (E-Gel) in the presence of electro-osmosis. The gas pressure forces the infusion of the drugs through appropriate means into the body with the pressure being dependent on the rate of electrolysis which in turn is controlled by an electric current. This means that the rate of drug delivery can be predetermined and precisely controlled under the action of an electronic timer or a biomedical control system.

The full content of US Patent 5,354,264 is hereby included herein by way of reference.

US Patent 5,354,264 indicates that the system is made possible through the use of a solid water swollen polymeric hydrogel network having negative charges along the polymer back bone or fixed within the polymer network. The system allows electro-conductivity to occur even when using pure water as the electrolyte. Pure water itself does not have electric conductivity compared to the saline solution taught in Gross et al. European Patent Application 0385915. With the negatively charged polymeric hydrogels of Insutech, Inc. electrical current can be conducted along the negative charges of the polymer backbone. The simple phenomena allows water electrolysis around the electrodes to generate hydrogen and oxygen gas only, free of chlorine or other gases which might be present in the case of saline or other solutions containing electrolyte ions.

Two principals governing the flow of water within the solid hydrogel network and the production of gases at the electrodes are discussed. Example 1 of US Patent 5,354,264 discloses a method of preparation of such a hydrogel.

Reference is also drawn to such transdermal and infusion devices as are disclosed in US Patent 4,969,874 (Disetronic Ag), US Patent 5,090,963 (Product Development (ZGS) Ltd), US 5,527,288 (Elan Medical Technologies Ltd), US 5,062,834 (Product Development (ZGS) Ltd), and US 5,156,591 (S.I. Scientific Innovations Ltd).

DISCLOSURE OF INVENTION

In a first aspect the present invention consists in a **substance delivery intra vaginal device** having an elongate body structure coupled to or having resilient means of variable geometry to facilitate in a target mammal vaginal tract insertion, to facilitate vaginal tract retention and to allow vaginal tract withdrawal, when the elongate axis of said body structure is substantially aligned to axis of the vaginal tract,

wherein said body has

a chamber to an outlet,

a bladder within said chamber sealed about said outlet to said body so as to be capable of delivering its contents via said outlet upon the application of gas pressure external of said bladder to the bladder, said bladder containing at least 5mL of said substance in a liquid delivery form, and

controlled or controllable gas generating means to generate a gas within said body so as to apply gas pressure within said chamber to the exterior of said bladder,

and wherein the gas generating means include

a hydrogel having electrolysis electrodes,

a battery powered circuit capable of applying a controlled or set current to said electrolysis electrodes so as to generate gas from the hydrogel which will have a pressurising effect on the exterior of said bladder,

switch means to allow energising of the circuit.

Preferably said substance is progesterone or a substance having a similar effect.

Preferably said substance is progesterone and the rate of expression enabled, whilst in the vaginal tract of a target mammal, by the content of the bladder, the outlet and the gas generating means is sufficient to first achieve a progesterone plasma level above 2 ng/mL and thereafter maintain a level of at least 2 ng/mL in the mammal for a period of at least 4 days.

Preferably the content of the bladder is from 1 to 60 mL of the delivery liquid.

Preferably said device has a removable seal or cap of said outlet (i) capable of being removed prior to intra vaginal insertion, (ii) which dissolves in the vaginal tract after insertion and/or (iii) which is rupturable under the pressure of the delivery liquid to be released after sufficient gas has been generated by said gas generating means after switch means energising of the circuit.

Preferably said switch means is a manually actuable switch externally accessible prior to the insertion of the device in the vaginal tract of a target mammal.

Preferably a tube or equivalent structure ("dip tube") providing a conduit to the outlet from within the bladder is provided thereby affecting the passive leakage rate of the delivery liquid from the device.

Preferably said dip tube is a plastics tube of circular cross-section less than 1mm in internal diameter.

Preferably said dip tube extends longitudinally of said body structure within said bladder.

Preferably said device includes a timer or a logic means which controls the provision of current to the electrolysis electrodes after actuation of said switch means.

Preferably said elongate body structure defines a second chamber in communication with said first chamber and said hydrogel is located in that second chamber.

Preferably said second chamber or an additional chamber locates the battery of said battery powered circuit.

Preferably said elongate body structure includes means remote from the outlet which facilitates the withdrawal of the device from the vaginal tract of a target mammal.

In another aspect the present invention consists in a substance delivery device (preferably of variable geometry for intra vaginal retention) having a reservoir of variable volume having an outlet (valved or otherwise), said reservoir containing the substance to

be delivered (preferably in an liquid form), the volume of the reservoir being reducible (preferably continuously) (and preferably from a volume greater than 1mL) under the action of either

i) a gas or gases generated by the application of a controlled or controllable electric current to a water containing matrix contained and/or carried by and/or otherwise associated with the device in such a way as generates free oxygen and free hydrogen (preferably without other gases), or

ii) a gas or gases generated by the electrolysis of water contained in a hydrogel contained and/or carried by the device (preferably a negatively charged hydrogel which enables hydrolysis of the water which does not otherwise contain free ionic species).

Preferably the source of electric current is from a battery contained by, carried or otherwise associated with the device.

Preferably said device is an intra-vaginal device including preferably a variable geometry construction which assists insertion and retention of the device in the vagina of a target species.

Preferably said device includes a plurality of such reservoirs of variable geometry each preferably each separately controlled insofar as the expression therefrom of its content is concerned.

Preferably the expression of progesterone or progesterone containing liquid is substantially continuous and preferably without being pulsile in nature.

Preferably said device includes a number of reservoirs of variable geometry and the substance to the delivered from at least one of the reservoirs of variable geometry is a progesterone.

Preferably the substance to be delivered from at least one other reservoir of variable geometry (whether solid, powder, in a liquid form, or otherwise) are active ingredients such as those hitherto discussed useful in conjunction with progesterone in controlling the synchrony of oestrus in mammals.

In still a further aspect the present invention consists in **a substance delivery device** having an assembly defining a reservoir of variable volume having an outlet (valved or otherwise), said reservoir containing the substance to be delivered (preferably in an liquid form), the volume of the reservoir being reducible (preferably continuously) (and preferably from a volume greater than 1mL) under the action of either

i) a gas or gases generated by the application of a controlled or controllable electric current to a water containing matrix contained and/or carried by and/or otherwise associated with the device in such a way as generates free oxygen and free hydrogen (preferably without other gases), or

ii) a gas or gases generated by the electrolysis of water contained in a hydrogel contained and/or carried by the device (preferably a negatively charged hydrogel which enables hydrolysis of the water which does not otherwise contain free ionic species).

Preferably said reservoir of variable geometry is at least in part defined by a bladder or flexible membrane.

Preferably the source of electric current is from a battery contained by, carried or otherwise associated with the device.

Preferably said device has a variable geometry construction which assists insertion and retention of the device in the vagina of a target species.

Preferably said device includes a plurality of such reservoirs of variable geometry each preferably each separately controlled insofar as the expression therefrom of its content is concerned.

In yet a further aspect the present invention consists in **an intra-vaginal device** of a kind having a generally elongate body and having at or adjacent one end thereof at least a plurality of arms capable of being moved between conditions which allows an easy insertion of the device as a whole into the vagina of a target species mammal and thereafter the reconfiguring thereof to provide the device in a varied geometry which resists spontaneous or accidental loss from the vaginal tract, the body of the device including means defining a reservoir of variable volume having an outlet (valved or otherwise), said reservoir containing the substance to be delivered (preferably in liquid form), the volume of the reservoir being reducible under the action of either

(i) a gas or gases generated by the application of a controlled or controllable electric current to a water containing matrix in such a way as generates free oxygen and free hydrogen (preferably without other gases), or

(ii) a gas or gases generated by the electrolysis of water contained in a hydrogel, the device also including a battery and appropriate circuitry to achieve the required end upon initiation of the device.

Preferably initiation can be by means of switching means (preferably once activated not able to be turned off accidentally **in vivo**) which activates a timer or a logic means (for example a micro processor or analog logic circuit).

Preferably the reservoir of variable geometry is a cylinder or other appropriate chamber having associated therewith a piston, plunger, membrane or the like capable directly or indirectly of being moved to pressurise the content of the chamber as a result of the gas generation.

Preferably said device delivers as at least one substance progesterone and preferably has an expression rate such as to achieve during a progesterone control of the animal, a

progesterone plasma level above 2 ng/mL after that level has been reached after initiation and/or introduction of the device.

In yet a further aspect the present invention consists in **a method of maintaining a progesterone plasma level above 2 ng/mL** which comprises inserting into the mammal an intra vaginal device capable of actively expressing from a chamber of variable geometry under the action of

(i) a gas or gases generated by the application of a controlled or controllable electric current to a water containing matrix in such a way as generates free oxygen and free hydrogen (preferably without other gases) or

(ii) a gas or gases generated by the electrolysis of water contained in a hydrogel; to thereby express progesterone at a rate which will first achieve a progesterone plasma level above 2 ng/mL and thereafter maintain a level there above (preferably without rapid fluctuations) at or above that level for a period of at least 4 days (preferably 5 or more).

Preferably the progesterone is expressible from a reservoir greater than 1mL in capacity (preferably 1 to 60mL).

In a further aspect the present invention consists in **an intra-vaginal device** suitable for controlling the synchrony of oestrus, said device comprising means which provides a single or multiple substance delivery therefrom, said device including a progesterone delivery means as described above.

As used hereinafter the term "body cavity" includes both fully enclosed and partially enclosed cavities. Examples include the rumen and the vagina but may be the chest cavity, etc.

In still a further aspect the invention consists in **a method of manufacturing a delivery device** useful in delivering at least one substance from the device when the device is implanted in or in a body cavity of a mammal, said method comprising the steps of

(i) using in at least one such mammal an active substance release device of a kind where at least one such substance is controlled continuously and/or continually as to its release, the release of at least one such substance being from an outlet (or outlets) from a reservoir of variable geometry which reduces controllably, the control being by means of the control of the provision of an electric current to a water containing matrix capable of generating free oxygen and free hydrogen when the current is applied to the water containing matrix via electrodes or the equivalent and determining the optimum release profile for the release of at least one such substance in order to elicit desired effect(s) in the mammal, and

(ii) thereafter preparing a substance delivery device capable of being implanted in or in a body cavity of a mammal of similar type which in use in a mammal through either

(a) an active substance release will substantially reproduce the optimum release profile determined by step (i), or

(b) a passive substance release **in vivo** will substantially reproduce the optimum release profile determined by step (i).

Preferably step (ii) is performed in such a way as to, **in vivo**, match the substance profile in the plasma of a targeted recipient for the device.

Preferably step (i) is performed using the device in a vaginal retainable form, the active ingredient being delivered into the vagina of the animal.

Preferably the substance is progesterone and the optimum profile preferably is to maintain for about 5 days or longer a progesterone plasma level of greater than 2 ng/mL.

BRIEF DESCRIPTION OF DRAWINGS

The present invention will now be described with reference to the accompanying drawings in which;

Figure 1 shows a series of drawings (a) through (e) of a prior art EaziBreed™ CIDR™ product of this company having a progesterone impregnated silicone matrix of an average depth of about 1.5mm but having the depth thereof varying greatly,

Figure 1A is an elevation of the "T" shaped device capable of having the top arms thereof resiliently bent to alongside the upstanding body during insertion with an appropriate applicator pull and capable of assuming some return to the "T" form so as to be retained within the vagina of an appropriate animal such as a cattle beast,

Figure 1B is a section at "FF" of the top arms of the "T" form,

Figure 1C is a section at "DD" of the body,

Figure 1D is a view "CC" of the end of the body showing a slot formed therein from a hole through the body so as to allow the lying therein of a retained withdrawal string or other device,

Figure 1E is a section of the body at "EE",

Figure 1' shows the preferred spine of the prior art device, a spine which with no or little modification is useful in a device in accordance with the present invention,

Figure 1'A shows an elevation of the spine,

Figure 1'B showing a side elevation of the spine,

Figure 1'C showing the plan view of the top arms of the device,

Figure 1'D shows the section at "AA",

Figure 1'E shows the section at "BB",

Figure 2 shows a CIDR-B™ form of passive device of this company (NZ Patent Specification No. 286492) having an average progesterone impregnated matrix of about

1mm thick over a spine of a kind shown in Figure 2,

Figure 2A shows an elevation of the device of Figure 3.

Figure 2B shows the side elevation of the device of Figure 3A,

Figure 2C shows a plan view of the top of the device as shown in Figures 3A and 3B,

Figure 2D shows a section at "JJ",

Figure 2E shows a section at "II",

Figure 2F shows a section at "KK",

Figure 2G shows a section at "GG", and

Figure 2H shows a section at "HH" being the hinging region of the arms from the body,

Figure 2I is the section "LL" of Figure 3A,

Figure 3 shows the prior art PRID™ device previously referred to,

Figure 3A shows the helical or coil form of the device having an optional capsule affixed thereto as previously stated, the device also showing a withdrawal string, and

Figure 3B shows an applicator tool for the device of Figure 3A,

Figure 4 is the plot for the CIDR-B™ device,

Figure 5 is the plot for the SMARTT*I*™ IBD,

Figure 6 is a device of the present invention substantially of the CIDR™ configuration having a large single reservoir dischargeable under the movement of a piston (less preferred) and variable geometry means to allow retention (eg; as an intra vaginal device),

Figure 7 shows in simple form a device for the release of an eroding matrix prior to the release of a drug or a matrix containing drug,

Figure 8 is a device for timed release after delay by the controller,

Figure 9 shows a device as in Figure 7 having a large single reservoir embodied in the stem of its general T form on one side and also having if desired an arrangement as depicted in Figure 7 in another part of the stem,

Figure 10 as in Figure 9 shows a multiple delivery system version of the device of Figure 7, Figure 10 having the arrangement of Figure 9 on the left hand side but substituting as a secondary delivery system that depicted in Figure 8, its being realised that a device that embodies the delivery system of Figure 6, Figure 7 and Figure 8 can be embodied in a single retention device for a body cavity as can other hybrid versions thereof,

Figure 11 is a preferred form of device (albeit not showing any intra-vaginal retention features) which uses a flexible membrane or bladder,

Figure 12 is the Figure 11 device in an intra-vaginal device form,

Figure 13 shows a device for insertion into the vagina the drug reservoir defined by a bladder in the internal cavity and upon which bladder the gas acts,

Figure 14 shows a device for insertion into the vagina similar to that of Figure 13 except that a conduit or tube from or which defines the outlet orifice extends back into the drug reservoir,

Figure 15 shows a device for insertion into the vagina, a rapid release mechanism being located within the arm of a retention wing preferably a breakable seal,

Figure 16 is a similar device to that of Figure 6 except it embodies the preferred use of a bladder as the means by which the drug reservoir is to be reduced in volume under the action of the generated gas,

Figure 17 shows the dip tube arrangement (e.g. as in Figure 14) but in a device as in Figure 16

Figure 18 is a preferred form of a device for single drug delivery also having a dip tube arrangement, the sequence of Figures 18A to 18D showing the mode of dispensing via the dip tube under the gas induced collapse of a latex bladder,

Figure 19 is a plot for the device of Figure 18A showing *in vitro* release rate of the device for two different currents to the gas generating hydrogel,

Figure 20 shows for a device of Figure 18A plasma progesterone levels (one with and one without a gas and control production unit) against the performance of a CIDR-B™ device of applicant,

Figure 21 shows the effect of the dip tube arrangement in a device such as in Figure 18A when there is no gas production and control unit thereby demonstrating vehicle retention/leakage *in vivo*,

Figures 22A and 22B show a resistor controlled circuits for providing current to the hydrogel electrodes,

Figure 23 is a plot showing for a hydrogel (E-gel) [upper plot] and aqueous NaCl [lower plot] plots of percent initial current as a function of time, and

Figures 24A and 24B show two forms of sealing arrangement for the outlet of a device as in Figure 18.

PRIOR ART

The prior art SMARTT *I*™ IBD is supplied packaged within a two part application container. Each part is manufactured from polypropylene plastic. The inner part is 89 mm in length, 39 mm (o.d.), 37 mm (i.d.) In diameter, and 1 mm in thickness. It has a hole in its base 26 mm in diameter through which the device and tail can protrude. The outer part is 120 mm in length, 1 mm in thickness and 41 mm (o.d.), 39 mm (i.d.) In diameter. It

tapers to a rounded shape at its top end. Groves are cut into the tapered round end allowing this part to flex open allowing the device to pass through it upon administration. Also attached to the outer part of the applicator container are hinged wings which rest against the device in the folded position. These wings are each 30 mm in length and designed to be opened, and rest upon the lips of the vulva, upon administration of the device. The SMARTT*I*™ IBD device fits snugly into the inner part of the application container which in turn fits snugly into the outer sheath of the device. Thus the application container affords protection of the SMARTT*I*™ IBD device on storage and handling and also holds the retention wings in a folded position during storage.

The SMARTT*I*™ IBD device itself comprises (i) an outer plastic sheath designed to protect the inner compartment and delicate electronics and (ii) the inner compartment which contains an electronic chip and board, has four drug reservoirs (one at the base of the device and three sited at the head of the device), engages a retention mechanism and has a tail.

The outer sheath is made of plastic (high density polyethylene) and is 131 mm in length and has a diameter of 25 mm at its upper opening. The outer sheath tapers about midway along its longitudinal length to a diameter of 20 mm. The bottom of the sheath has 5 mm diameter hole to allow the tail to pass through. The tail of plastic (high density polyethylene) and extends 226 mm behind the device and is 2 mm in diameter and appears relatively inflexible. At the terminal end of the tail is a flattened portion 22 mm in length, 5 mm wide and 2 mm deep. Integrated into the moulding of the tail at its top end is a round plug containing grips. This plus is designed to fit tightly into the base of the device and the grips are designed to prevent it falling out. This mechanism fixes the tail to the device and prevents it from loss during storage, when activated and during removal from the animal.

The retention mechanism comprises eight fixed prongs made from Hytrel evolving from a central circle each at an angle of 40°. Each prong is 51 mm in length and 2mm deep by 3.5 mm wide. At the terminal end of each prong is a circular protective ball 6 mm in diameter. This ball affords protection to the delicate vaginal mucosa during the insertion and retention of the device during the treatment period. The retention mechanism is located at the head of the device.

The inner compartment contains a "large" drug reservoir that runs approximately half the length of the device. At the top end of the reservoir is a small orifice which is opened and closed by a switch mechanism which is operated by a solenoid. In the closed position the switch is designed to prevent drug solution from leaving the drug reservoir. In the open position drug solution is allowed to freely flow through a small orifice which leads to a small bore stainless steel opening (absolute diameter unknown but <0.45 mm

i.d.). To the exterior at the flat face of the head of the device. This large drug reservoir is circular in shape, 18 mm in diameter and 22 mm in length. It has a capacity to hold a total volume of 5 mL of distilled water. The solution is prevented from escaping from the bottom of the device by a tight fitting SANTOPRENE rubber seal. Between the rubber seal and the bottom of the device is a movable plunger and spring which is 80 mm in length when uncoiled and of unknown tension. The device has been designed to allow the organic solution to be released from this large drug reservoir over a 10 day period.

Three other drug reservoirs are in the device (the "small reservoirs"). The reservoirs are located at the head of the device. They are sited equidistant around the flat face of the head of the device and are each of equivalent shape and size being ovoid in shape, 7.5 mm wide and 5 mm across and 16 mm in depth (with the rubber seal in place; 19 mm with the seal removed). Each of these drug reservoirs has the capacity to hold a total volume of 0.45 mL of distilled water (with the rubber seal in place). Drug solutions are prevented from leaking from the small reservoirs during storage and while in the animal by tight fitting rubber SANTOPRENE rubber) seals located at the head of the device (Figure 8). Only two of the small drug reservoirs are utilised and contain drug solutions in the SMARTT*I*™ IBD device.

The remainder of the device comprises a circuit board and 2 batteries (Type AAA) lying parallel with and under to the left and right of the circuit board. The circuit board contains components primarily consisting of a controlling chip, a power-on indicating LED and a quartz timer.

A plastic tag of variable length and 8 mm width is inserted between the positive end of the left AAA battery and the battery terminal of the device. It is of sufficient length to protrude beyond the head of the device. Removal of this tag activates the device. The circuit board and the battery terminals are coated in a generous layer of silicone grease to prevent moisture coming into contact with the electronic componentry of the device.

To operate the device in the field the device must first be removed from the applicator container in order to turn it on. In addition, to achieve activation of the device, the device itself must be dismantled. This entails partial removal of the outer sheath to enable removal of the plastic strip. After re-assembly of the outer plastic sheath onto the inner compartment and locking it over the retaining clamps, the device is then re-inserted into the applicator container and loaded onto the applicator gun. The rounded end of the applicator container is then lightly lubricated and pushed approximately 30 mm inside the vagina until the wings of the application container lie flush with the lips of the vulva. Pressure is then applied to the device by pushing the applicator gun. This results in the device being inserted into the anterior vaginal close to the cervix. To remove the device

at the end of the treatment period the protruding tail is pulled gently but firmly until the device is removed.

Table 3. Summary of the three drug reservoir vehicles

Reservoir	Vehicle odour	Vehicle colour	Active agent as stated by Plade Holdings
Large	Benzaldehyde	Straw	Progesterone
Small reservoir 1	Alcoholic	Clear	Oestradiol benzoate
Small reservoir 2	Aniseed	Clear	Cloprostenol sodium
Small reservoir 3	Empty	Empty	Empty

Mechanism of oestradiol benzoate and cloprostenol sodium release from the SMARTT*I*™ IBD

The contents of the small reservoirs are found to be released by the following mechanism. The reservoirs contain a spring loaded plunger which is pulled back and held in the loaded position. This is achieved by locking it in place by a retaining cord which rests over a resistor located on the electronic board. The resistor located under the cord retaining the plunger is activated at a pre-programmed time under the control of the circuit board chip. Upon activation the resistor heats up and the cord burns through and severs. The plunger is therefore no longer under tension and the contents of the reservoir are violently expelled by the sudden relaxing of the spring pushing against the plunger.

Mechanism of progesterone release from the SMARTT*I*™ IBD

The mechanism of release of the progesterone containing vehicle relies upon (i) a large spring located at the base of the device which forces a moveable plunger through the reservoir, (ii) a small orifice and (iii) a solenoid. Progesterone containing vehicle is released through a small orifice which leads to a length of small bore tubing which opens at the head of the device. The opening and closing of the orifice controls how much vehicle is released and this in turn is controlled by a solenoid which opens and closes the small orifice. When the solenoid is activated the closure pulls back against the force of a small spring and opens the orifice that leads to the small bore tubing. The frequency of opening and closing of the orifice follows a pre-defined program which is controlled by the micro chip. When the solenoid is activated the orifice opens during which time the progesterone containing vehicle is allowed to travel through the orifice, up the small bore tubing and out of the opening at the head of the device. When the solenoid is turned off a small spring pushes forward and seals the opening and no progesterone release occurs.

Plasma levels of progesterone following 12 day insertion of the SMARTT*I*™ IBD device

The plasma progesterone levels for six ovariectomised cows with SMARTT*I*™ IBD inserted for 12 days are shown in Figure 5. The profiles for each device typically show an initial rise in plasma progesterone levels immediately following insertion (the magnitude of which shows considerable variation between animals), decreasing to concentrations close to basal levels on about day 4. Plasma levels then remain at this low level until device removal.

Deliveries from Small Reservoirs of the SMARTT*I*™ IBD device

In vitro trialing showed reliable release at preprogrammed times. Reliability **in vivo** inconclusive owing to unreliability of the progesterone deliveries and their effects on the recipient animals.

THE PRESENT INVENTION

The pump system of the present invention occupying less space could replace much of the pumping mechanism of the SMARTT*I*™ eg. plunger, spring and solenoid, and thereby can increase the drug reservoir to 60 mL or more.

The following table (Table 4) outlines parameters in respect of the progesterone delivery aspects, a preferred device of the present invention preferably operates at:

TABLE 4

Parameter	Value
dose rate (mg/day)	70
period (days)	5
total volume (mL)	8
delivery rate (mL/day)	1.6
pump rate (mL/hr)	0.07

The CIDR-B™ delivers progesterone at a rate of approximately 70 mg/day.

A device of the present invention is believed to achieve the following delivery rates (Table 5).

TABLE 5

Infusion (70 mg/day)	Delivery rate (mL/hr)
i.v. emulsion (0.67 mg/mL)	~5
i.vag. Emulsion (0.67 mg/mL)	~5
i.vag alcoholic solution (0.1 mg/mL)	~30
i.vag aqueous solution (0.01 mg/mL)	~300

It has been suggested that the device could be provided with reservoirs used for the pulsile delivery of drugs, immediately on and/or a number of days after administration.

The present invention is depicted in a number of different embodiments in Figures 6 through 16.

In these drawings the reference numerals denote the following;

(1) drug reservoir chamber,

(2) outlet (preferably simply a small opening or alternatively a one way valved opening or an opening from which a cover has been removed prior to initiation)

(3) stopper, plunger, piston or the like (could be a membrane in some forms),

(4) a gel of the kind previously described,

(5) a controller device embodying the appropriate logic circuit (analogue or microprocessor) preferably having source of power, (eg; one or more batteries) and providing appropriate energisation as required to the electrodes,

(6) the electrodes,

(7) a switch preferably capable of being activated simply to initiate the device prior to insertion,

(8) is a matrix containing drug (preferably liquid but not necessarily so),

(9) a matrix not containing the drug,

(10) a seal capable of being disrupted by movement of the piston, plunger or the like 4 under the action of the gel 5,

(11) drug reservoir bladder.

Figure 6 shows a device for insertion into the vagina with an outlet orifice 2 for the expulsion of vehicle from a reservoir 1 formed by an internal cavity in the body of the device, with a plunger 3 positioned in the reservoir, behind which is an electrolytic cell 4 for the production of gas to activate the plunger, with electrodes 5 inserted into the electrolytic cell, the production of gas being controlled and powered by the electronic control and power supply unit 6 which is activated by a switch 7.

Figure 7 shows a device for the rapid release of a pharmaceutical formulation retained behind a breakable seal 16.

Figure 9 shows the positioning of a rapid release device of Figure 7 within a device for insertion into the vagina, the other release device/devices being (e.g.) as in Figure 6.

Figure 11 shows a simple bladder or membrane (broken line) 11 capable without any jamming prospect of dispensing a liquid through outlet 12 under the action of the E-Gel and electrode generated gases within the housing 13. The E-Gel 14 electrodes are powered and controlled from sealed control chamber 15.

The Figure 11 design responds to very low rates of gas production. Piston including devices have required greater pressures to function.

Figure 12 is a device of Figure 11 in an intra-vaginal device form.

Figure 13 shows a device for insertion into the vagina with the drug reservoir defined by a bladder in the internal cavity and upon which bladder 11 gas activates.

Figure 14 shows a device for insertion into the vagina with the outlet orifice being defined by or being at the upper end of a dip tube (conduit or the like) 17. This tube will have some effect on feed out rate as the gas is generated and, if sufficiently strong, will favour radial collapse of the bladder 11 about the tube 17.

Figure 15 shows a device for insertion into the vagina with a rapid release mechanism located within the arm of the wing of retention means preferably behind a breakable seal 18.

Figure 16 is the preferred bladder form of the device of Figure 6, the bladder being 11.

Figure 17 is the dip tube (17) variant of the device of Figure 16.

Figure 18 shows a preferred form of the device where a single vehicle is to be released via a dip tube 17 whilst being retained in the vagina by variable geometry wing or the equivalent 18, the device being of a kind having a collapsible latex bladder 19.

Preferred dimensions of the Figure 18 device are:

- length of body - from 50 to 250 mm, preferably 150 mm.
- length of wings - from 40 to 250 mm, preferably 150 mm.
- diameter of body - from 5 to 60 mm, preferably 25 mm.
- material of body - a rigid material such as rigid PVC tubing.
- materials of wings - a rigid material such as PVC, or a material with a degree of softness such as silicone rubber.

Preferred hydrogel material and volume for a device of Figure 18 are:

- volume - from 0.1 to 50 mL, preferably 1 mL.
- material - a polymer or combination of polymers possessing gelling abilities and negatively charged groups, preferably agarose (obtainable from Sigma Chemical Co, USA - Product code A-6013) and dextran sulfate (obtainable from Sigma Chemical Co. USA - Product code D-4911).

Figures 18A through 18D shows the collapse sequence customarily expected from a device of this kind.

Figure 19 shows the *in vitro* release rate of a liquid vehicle from a device as shown in Figure 18 using two different currents and thus rates of gas production. In the plot of cumulative volume released (millilitres) against time (days) a lower current of 250 mA is shown below an upper line for a current of 500 mA.

The rate of gas produced during electrolysis in an electrolytic cell is proportional to the applied current. Therefore a constant current is required to achieve a constant and controlled rate of gas production. Figure 23 displays the current observed through two types of electrolytic cell (using a circuit as per Figure 22A) over a period of 7 days. The current through an electrolytic cell containing the hydrogel was observed to be constant, varying by less than 6% of the initial (t=0) current, suggesting a controlled rate of gas production. However current through an electrolytic cell containing saline (NaCl) was observed to steadily decline over the observation period by 14% of the initial (t=0) current, suggesting a decreasing and thus uncontrolled rate of gas production.

Figure 20 shows on a plot of progesterone plasma levels (mg/mL) against time after

insertion of the device in days. The line "A" is of a device as shown in Figure 18 without a gas production and control unit. The lines "B" and "C" are two plots of the performance of a device as shown in Figure 18 each with a gas production and control unit. By way of comparison the line "D" shows the performance of a conventional CIDR-B™ device of this company.

Intra vaginal delivery devices of the type shown in Figure 18 that do not possess a dip tube passively release vehicle contained in the bladder at such a rate that after a 7 day insertion period in the vagina of cattle approximately 80% of the initial volume of vehicle is released. This has implications on the ability to control the release of vehicle by controlling the rate of gas production (ie; current) and therefore the flow rate of vehicle. Devices that do not possess a dip tube can not delivery vehicle *in vivo* at the same rate observed *in vitro* (see Table 6). Therefore passive leakage should be kept to a minimum in order to differentiate between selected currents and therefore flow rate of vehicle. Acceptable minimum passive release is less than 20% of the initial volume of vehicle over any insertion period.

TABLE 6

In vitro release rate (mL)	Current (mA)		In vivo release of vehicle after a 7 day insertion period (mL)		
	Initial	Final	Initial	Final	Release
1	0.25	0.24 ± 0.01	13.5 ± 0.7	1.8 ± 2.1	11.7 ± 1.6
2	0.50	0.53 ± 0.02	14.8 ± 0.8	0.1 ± 0.0	14.7 ± 0.7

Figure 21 shows the effect of a dip tube arrangement upon the *in vivo* retention of vehicle when there is no gas production and control unit. If no dip tube arrangement is present as depicted by the lower end approximately 80% of the vehicle is lost *in vivo* due to passive leaking from the delivery orifice. This is to be compared with the upper line which shows the same apparatus but with a dip tube arrangement as shown in Figure 18A present. In this instance only about 30 - 40% of the vehicle is lost owing to passive leaking.

Figures 22A and 22B show a simple circuit to the electrodes of the hydrogel H, the circuits have in each instance a battery B (of any suitable kind) and a fixed resistor R or a variable resistor VR.

Figures 24A and 24B show preferred methods of sealing the delivery outlet of devices of the type shown in Figure 18. Figure 24A shows a plug "P" that is inserted into the delivery outlet and is designed such that a closed fitting seal is created. A tag or

suitable means can also incorporated for removal of the plug. Figure 24B shows a tag or film T that is placed over the delivery outlet, the film may be retained by means of a suitable adhesive. Removal of the tag is achieved when the overlapping edges of the tag are pulled away from the delivery outlet immediately prior to intra vaginal insertion.

A feature of the present invention is the simplicity of each delivery aspect within the retention body and the prospect to improve the volume available from which active ingredient can be expressed. With the preferred embodiments the simplicity of the arrangements within the retention device ensures the prospect of locating the liquid sensitive components at an end of the device away from the liquids to be dispensed unlike the prior art devices discussed.

The active substances are released from the syringe type variable volume reservoir under the action of the gases generated from the gel under the energisation from the controller. The overall arrangement is such that the pump aspect itself (the gel and its energising controller) contains no moving parts.

The pump aspect is able to act upon the piston plunger or the like of the syringe type dispenser in a continuous manner thereby ensuring constant non pulsile release of drug from the outlet of the device. As a consequence it is possible to achieve a constant plasma concentration of drug. If the action of the pump where non constant, (ie; on and off periods of action and inactivity) the on/off nature would result in a non constant plasma concentration profile.

By using an inert matrix that sloughs off under the normal mechanical actions (see Figure 7) the drug matrix would not be available to exert an effect until the inert matrix slug has been expelled.

Also the variant of Figure 8 includes a delay timing mechanism reliant on the controller ie; would force seal 10 open as required.

The present invention therefore by avoiding an on/off dispensing can in preferred embodiments provide the optimum plasma profiling and much greater reliability owing to less likelihood of plunger or piston jamming. As a result of the simplicity of the layout within the device which allows a better isolation of the sensitive controller components from the environment.

The continuous uninterrupted pumping ability of the devices of the present invention and the simplicity of construction is believed will find favour with farmers.

The devices of the present invention can also be programmed to investigate optimum blood serum levels (eg; progesterone et al) relevant (eg; to synchronisation) and that data then be used either to program devices for general sale or to be used with a view to matching passive devices to that desired outcome.

CLAIMS:

1. **A substance delivery intra vaginal device** having an elongate body structure coupled to or having resilient means of variable geometry to facilitate in a target mammal vaginal tract insertion, to facilitate vaginal tract retention and to allow vaginal tract withdrawal, when the elongate axis of said body structure is substantially aligned to axis of the vaginal tract,

wherein said body has

a chamber to an outlet,

a bladder within said chamber sealed about said outlet to said body so as to be capable of delivering its contents via said outlet upon the application of gas pressure external of said bladder to the bladder, said bladder containing at least 5mL of said substance in a liquid delivery form, and

controlled or controllable gas generating means to generate a gas within said body so as to apply gas pressure within said chamber to the exterior of said bladder,

and wherein the gas generating means include

a hydrogel having electrolysis electrodes,

a battery powered circuit capable of applying a controlled or set current to said electrolysis electrodes so as to generate gas from the hydrogel which will have a pressurising effect on the exterior of said bladder,

switch means to allow energising of the circuit.

2. A device of claim 1 wherein said substance is progesterone or a substance having a similar effect.

3. A device of claim 1 or 2 wherein said substance is progesterone and the rate of expression enabled, whilst in the vaginal tract of a target mammal, by the content of the bladder, the outlet and the gas generating means is sufficient to first achieve a progesterone plasma level above 2 ng/mL and thereafter maintain a level of at least 2 ng/mL in the mammal for a period of at least 4 days.

4. A device of claim 3 wherein the content of the bladder is from 1 to 60 mL of the delivery liquid.

5. A device as claimed in any one of the preceding claims wherein said device has a removable seal or cap of said outlet (i) capable of being removed prior to intra vaginal insertion, (ii) which dissolves in the vaginal tract after insertion and/or (iii) which is rupturable under the pressure of the delivery liquid to be released after sufficient gas has been generated by said gas generating means after switch means energising of the circuit.

6. A device as claimed in any one of the preceding claims wherein said switch means is a manually actuable switch externally accessible prior to the insertion of the device in the

vaginal tract of a target mammal.

7. A device as claimed in any one of the preceding claims wherein a tube or equivalent structure ("dip tube") providing a conduit to the outlet from within the bladder is provided thereby affecting the passive leakage rate of the delivery liquid from the device.

8. A device of claim 7 wherein said dip tube is a plastics tube of circular cross-section less than 1mm in internal diameter.

9. A device of claim 7 or 8 wherein said dip tube extends longitudinally of said body structure within said bladder.

10. A device as claimed in any one of the preceding claims wherein said device includes a timer or a logic means which controls the provision of current to the electrolysis electrodes after actuation of said switch means.

11. A device as claimed in any one of the preceding claims wherein said elongate body structure defines a second chamber in communication with said first chamber and said hydrogel is located in that second chamber.

12. A device as claimed in claim 11 wherein said second chamber or an additional chamber locates the battery of said battery powered circuit.

13. A device as claimed in any one of the preceding claims wherein said elongate body structure includes means remote from the outlet which facilitates the withdrawal of the device from the vaginal tract of a target mammal.

14. **An intra-vaginal device** of a kind having a generally elongate body and having at or adjacent one end thereof at least a plurality of arms capable of being moved between conditions which allows an easy insertion of the device as a whole into the vagina of a target species mammal and thereafter the reconfiguring thereof to provide the device in a varied geometry which resists spontaneous or accidental loss from the vaginal tract, the body of the device including a bladder defining a reservoir of variable volume having an outlet (valved or otherwise), said reservoir containing the substance to be delivered in liquid form, the volume of the reservoir being reducible under the action of either

i) a gas or gases generated by the application of a controlled or controllable electric current to a water containing matrix in such a way as generates free oxygen and free hydrogen, or

ii) a gas or gases generated by the electrolysis of water contained in a hydrogel, the device also including a battery and appropriate circuitry to achieve the required end upon initiation of the device.

15. **A method of maintaining a progesterone plasma level above 2 ng/mL** in a target species mammal which comprises inserting into the mammal an intra vaginal device

capable of actively expressing from a chamber of variable geometry under the action of

(i) a gas or gases generated by the application of a controlled or controllable electric current to a water containing matrix in such a way as generates free oxygen and free hydrogen, or

(ii) a gas or gases generated by the electrolysis of water contained in a hydrogel; to thereby express progesterone at a rate which will first achieve a progesterone plasma level above 2 ng/mL and thereafter maintain a level there above at or above that level for a period of at least 4 days.

16. An intra-vaginal device suitable for controlling the synchrony of oestrus, said device comprising means which provides a single or multiple substance delivery therefrom, said device also being a device as claimed in any one of claims 1 to 14.

17. **A method of manufacturing a delivery device** useful in delivering at least one substance from the device when the device is implanted in a body cavity of a target species mammal, said method comprising the steps of

(i) using in at least one such mammal an active substance release intra vaginal device of a kind where at least one such substance is controlled continuously and/or continually as to its release, the release of at least one such substance being from an outlet (or outlets) from a reservoir of variable geometry which reduces controllably, the control being by means of the control of the provision of an electric current to a water containing matrix capable of generating free oxygen and free hydrogen when the current is applied to the water containing matrix via electrodes or the equivalent and determining the optimum release profile for the release of at least one such substance in order to elicit desired effect(s) in the mammal, and

(ii) thereafter preparing a substance delivery device capable of being implanted in or in a body cavity of a mammal of similar type which in use in a mammal through either

(a) an active substance release, or (b) a passive substance release **in vivo** will substantially reproduce the optimum release profile determined by step (i).

18. A method of claim 17 wherein step (ii) is performed in such a way as to, **in vivo**, match the substance profile in the plasma of a targeted recipient for the device.

19. A method of claims 17 or 18 wherein the device is to be an intra vaginal device and step (i) is performed using the device in a vaginal retainable form, the active ingredient being delivered into the vagina of the animal.

20. A method as claimed in any one of claims 17 to 19 wherein the substance is

progesterone and the optimum profile preferably is to maintain for about 5 days or longer a progesterone plasma level of greater than 2 ng/mL.

21. A method of any one of claims 17 to 20 wherein the device resulting from step (ii) is a device as claimed in any one of claims 1 to 14 and 16.

22. An intra vaginal device substantially as hereinbefore described with reference to any one or more of the accompanying drawings being a device as claimed in any one of claims 1 to 14 and 16.

FIG 1

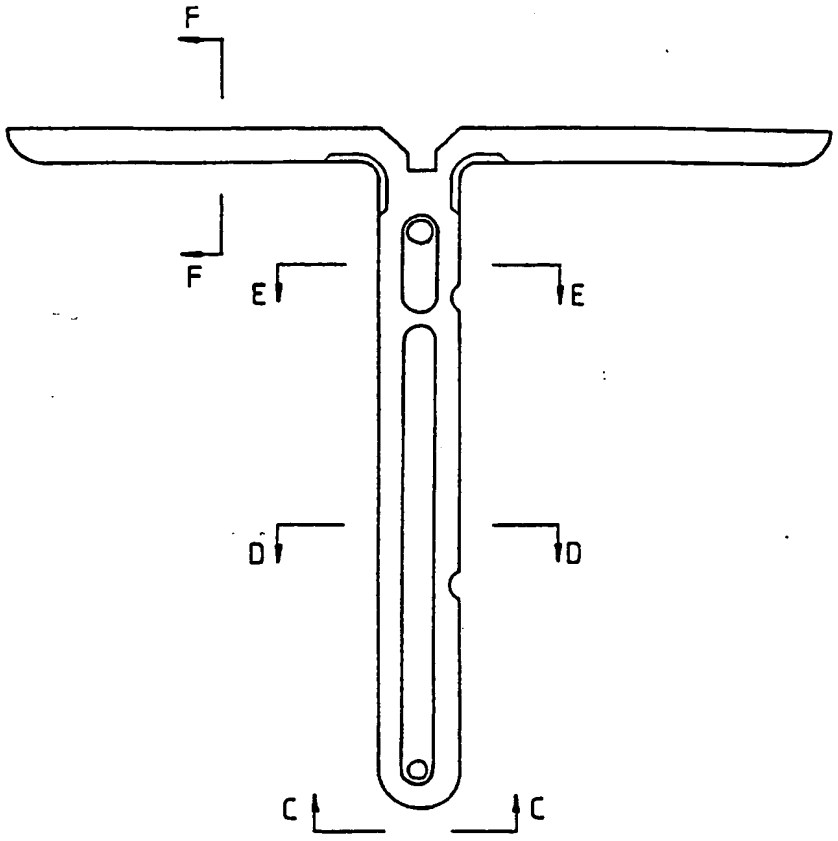


FIG 1A

FIG 1B

FIG 1C

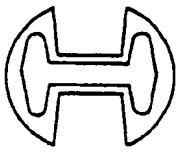


FIG 1D

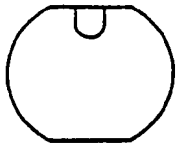


FIG 1E

FIG 1'

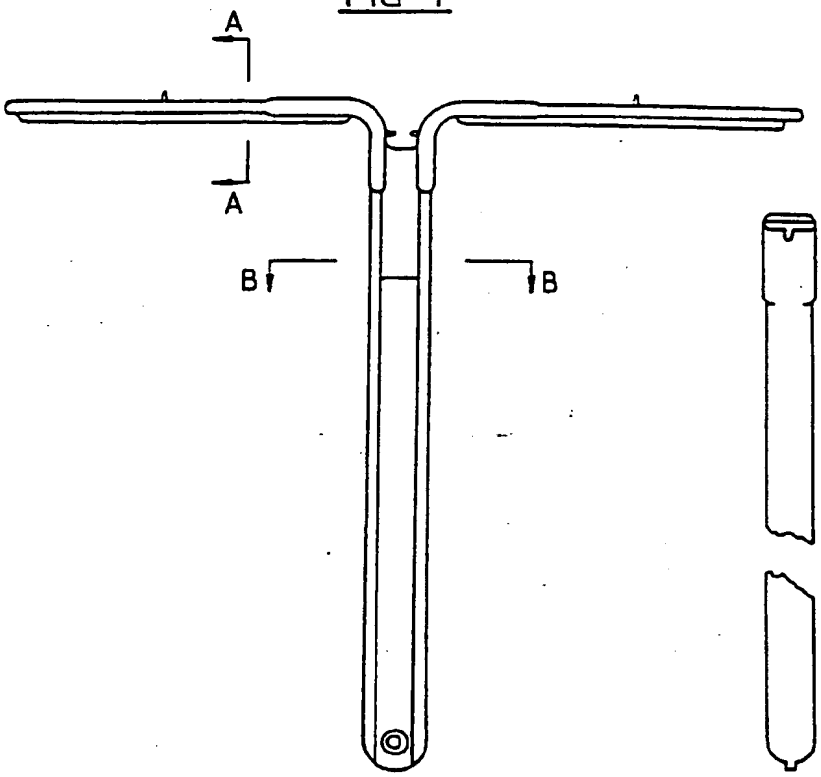


FIG 1'A

FIG 1'B

FIG 1'C

FIG 1'D

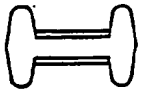


FIG 1'E

FIG 2

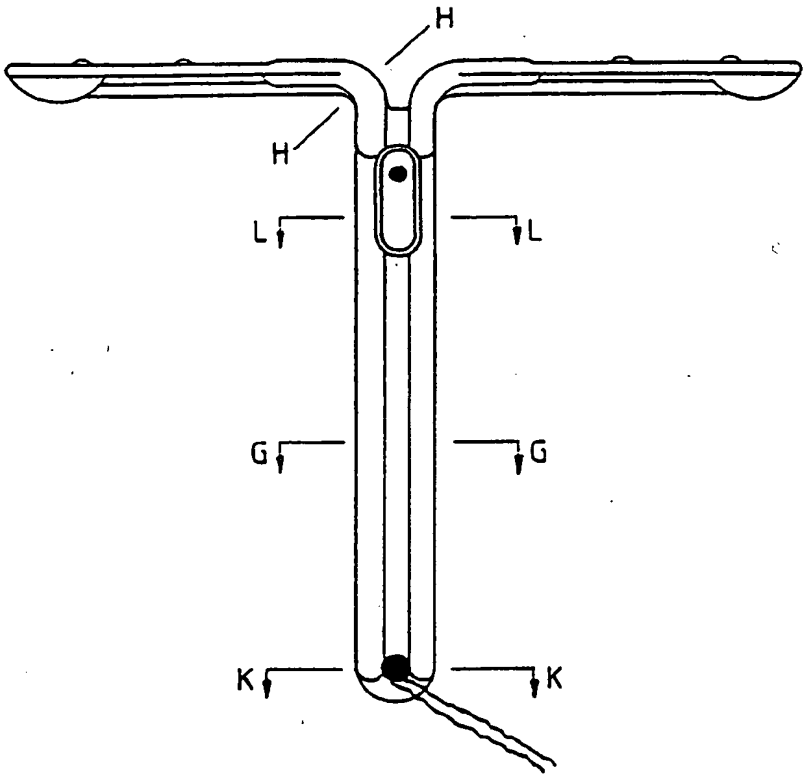


FIG 2A

FIG 2B

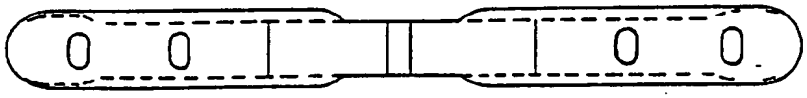


FIG 2C

FIG 2E

FIG 2D

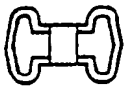


FIG 2F

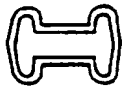


FIG 2G

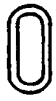


FIG 2H

FIG 2I

FIG 3A

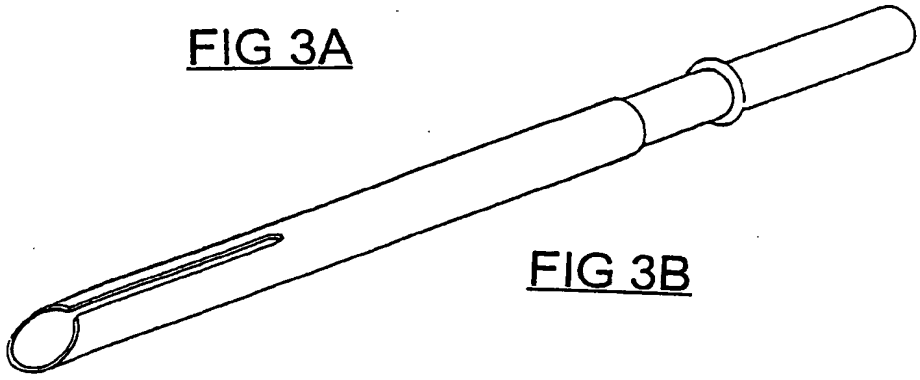


FIG 3B

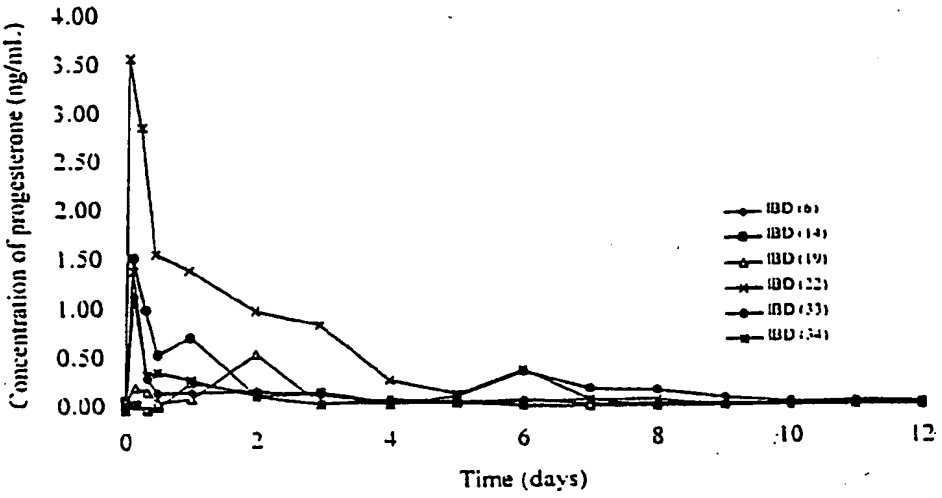


FIG 5 Plasma progesterone levels for individual ovariectomised cows with SMARTT*I*™ IBD inserted for 12 days.

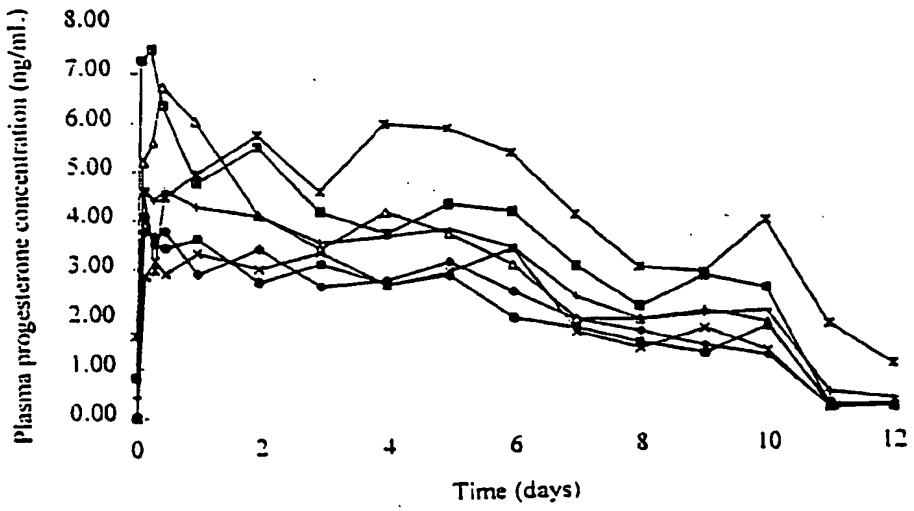


FIG 4 Plasma progesterone levels for individual ovariectomised cows with CIDR-B devices inserted for 10 days.

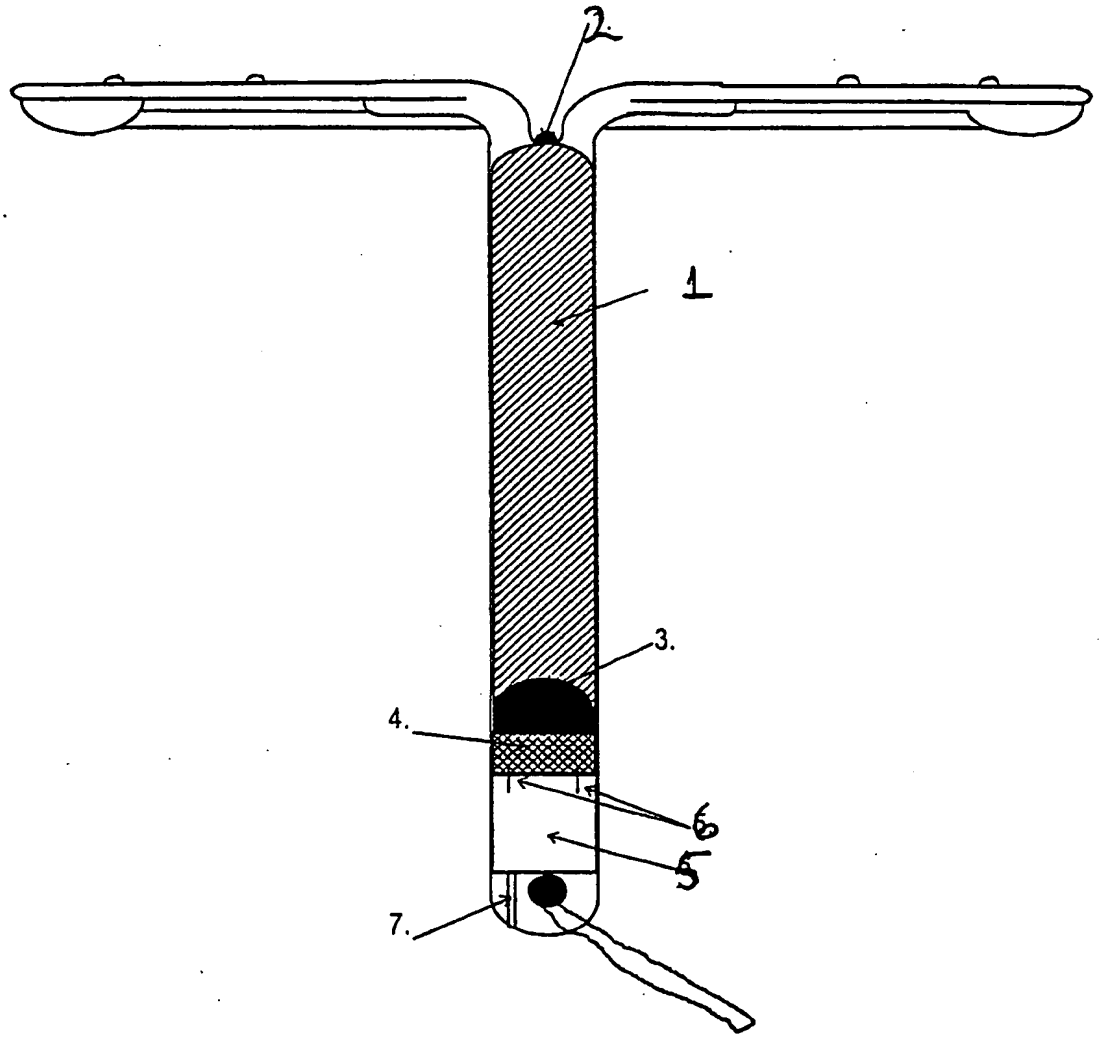


FIG 6

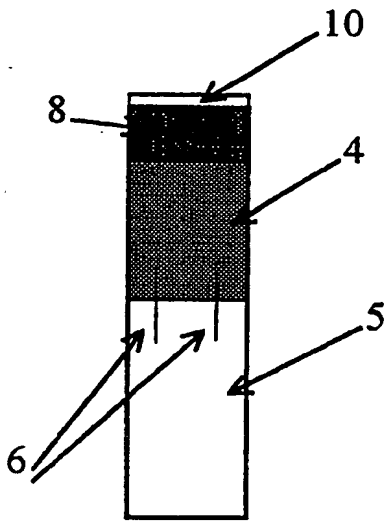


FIG 8

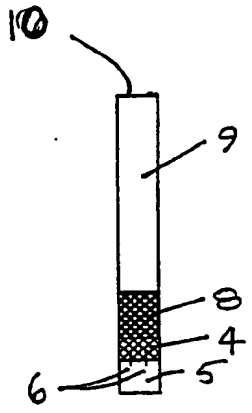


FIG 7

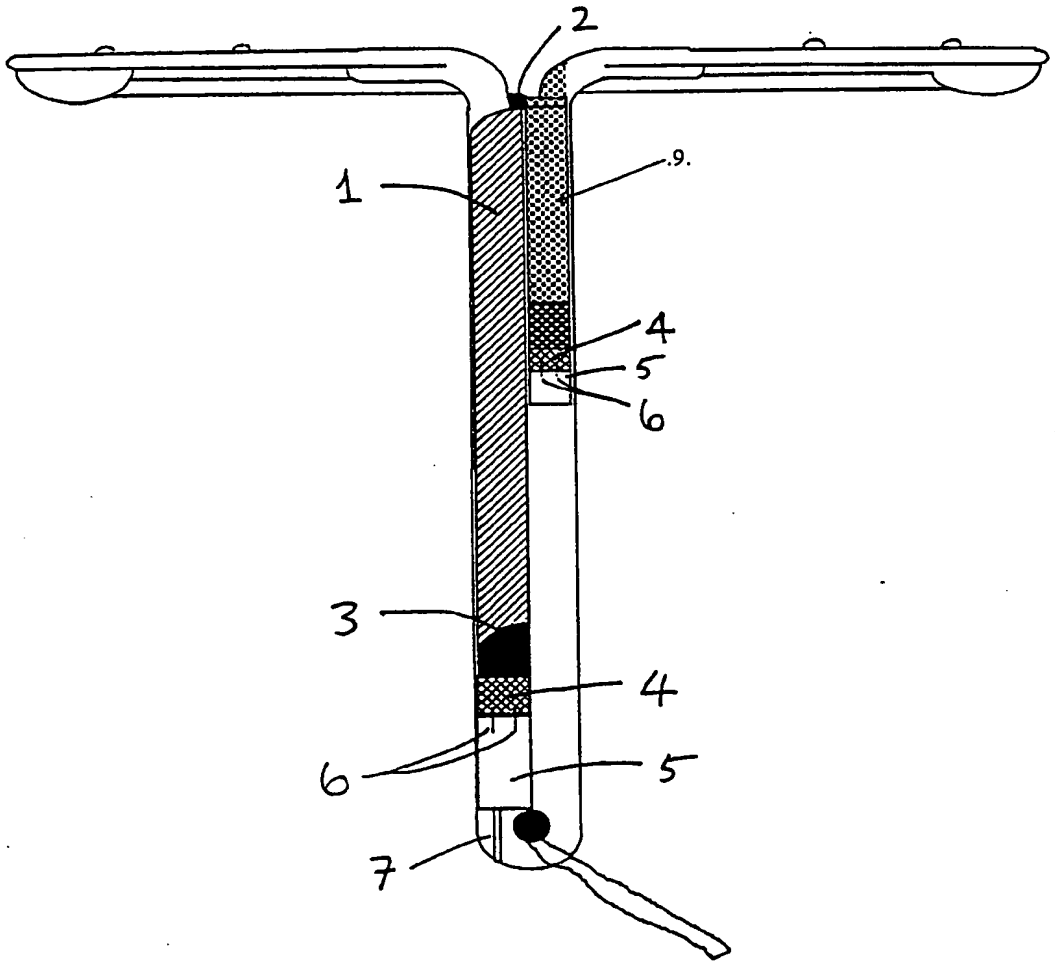


FIG 9

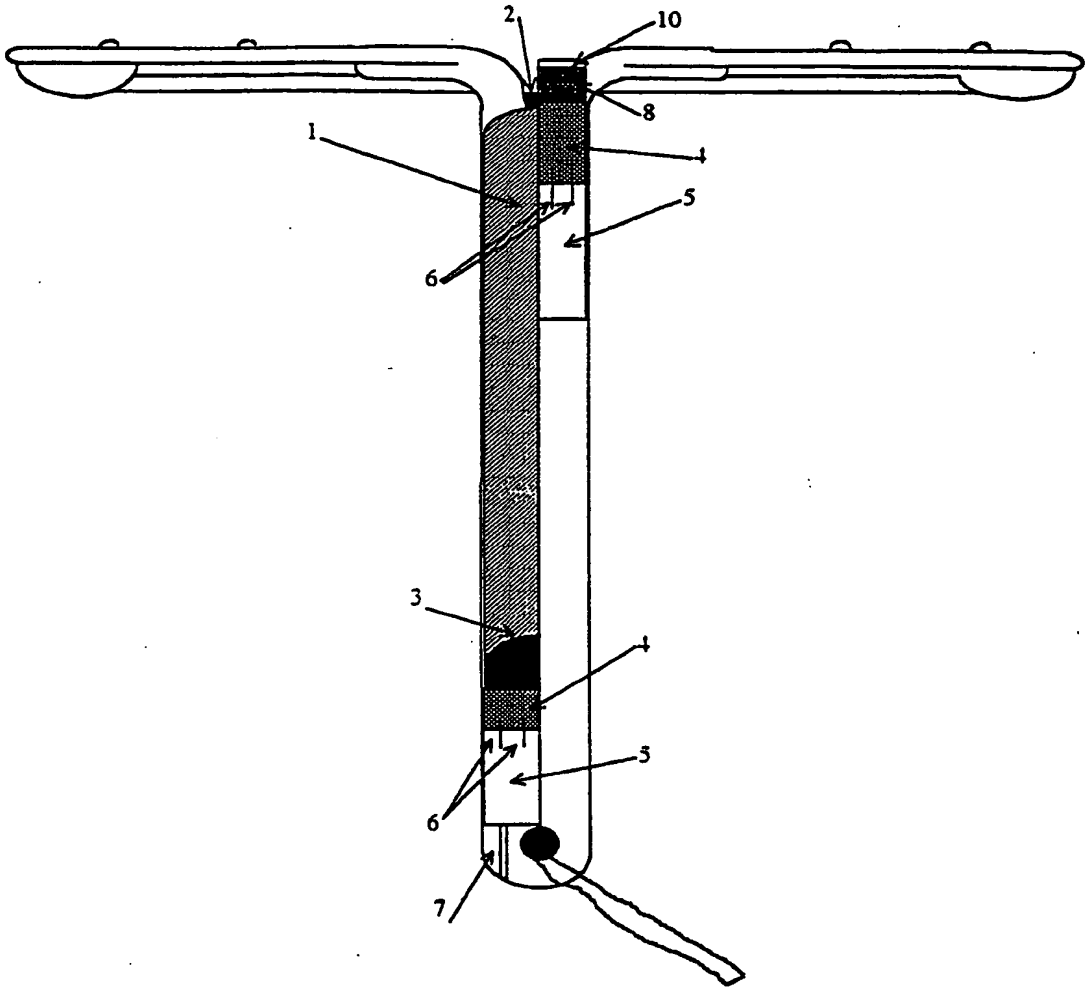
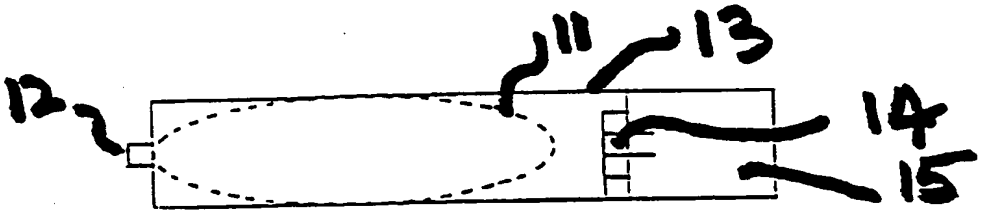


FIG 10

FIG 11



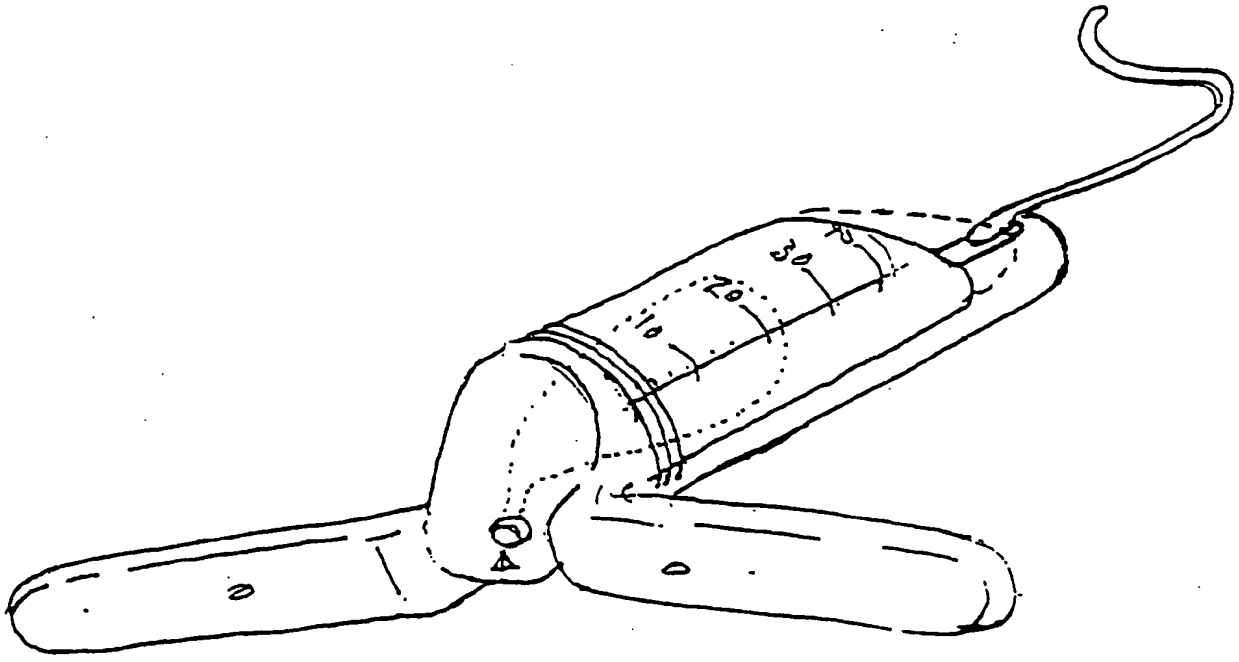


FIG 12

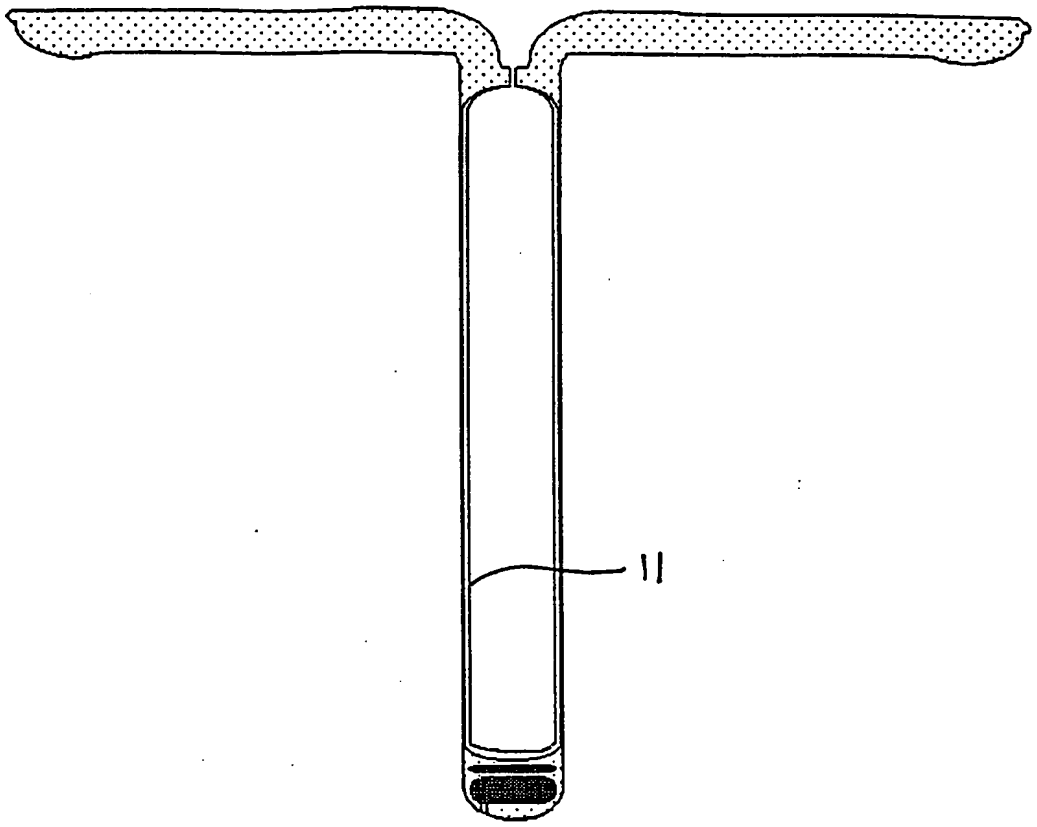


FIG 13

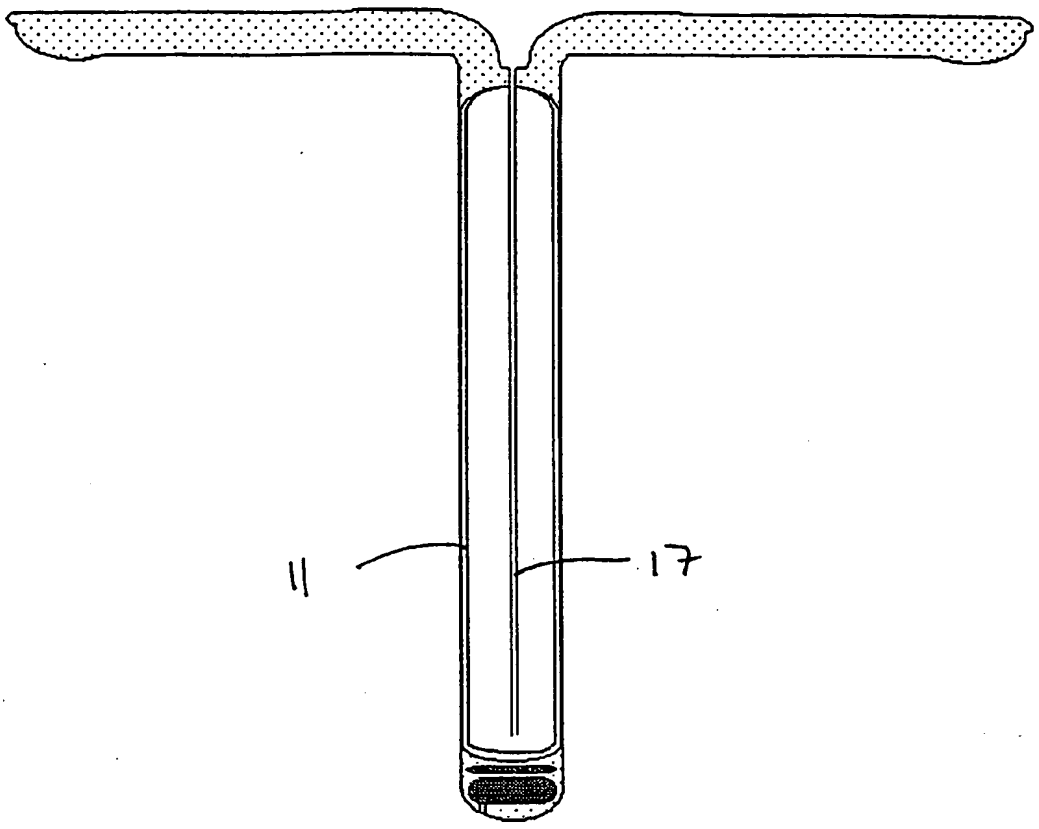


FIG 14

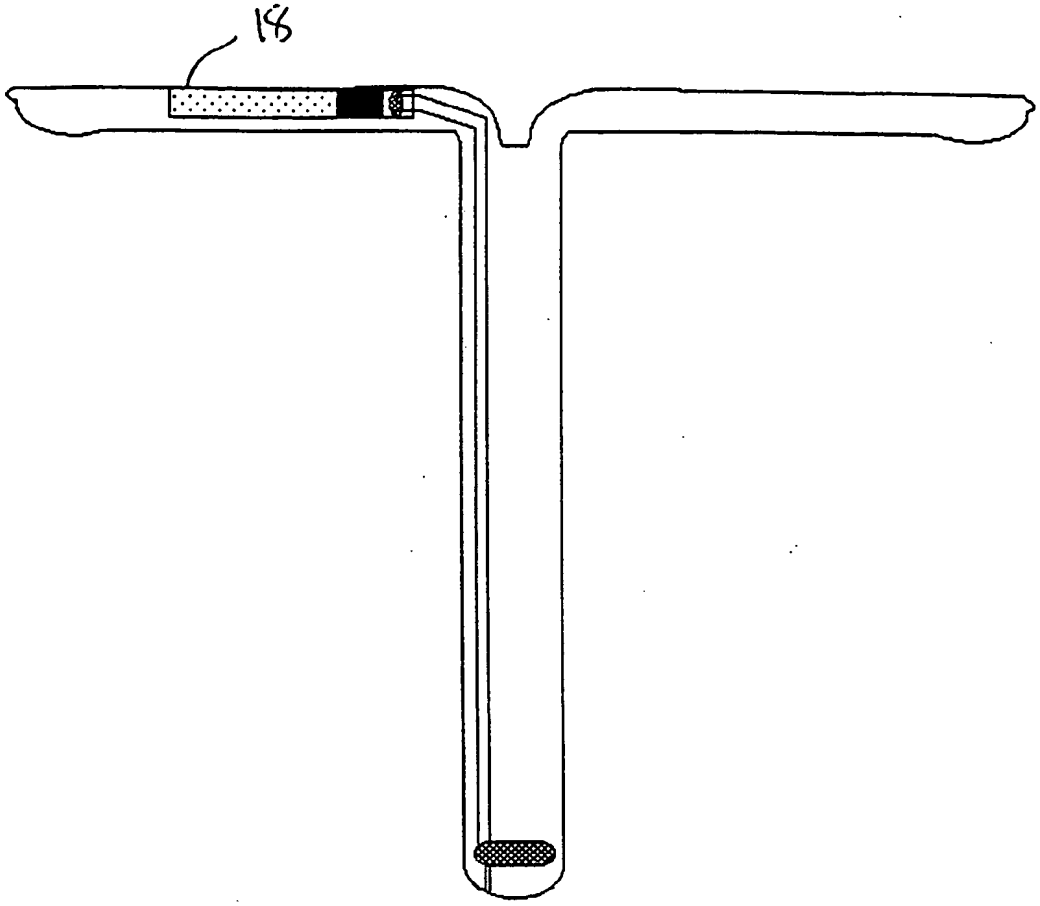


FIG 15

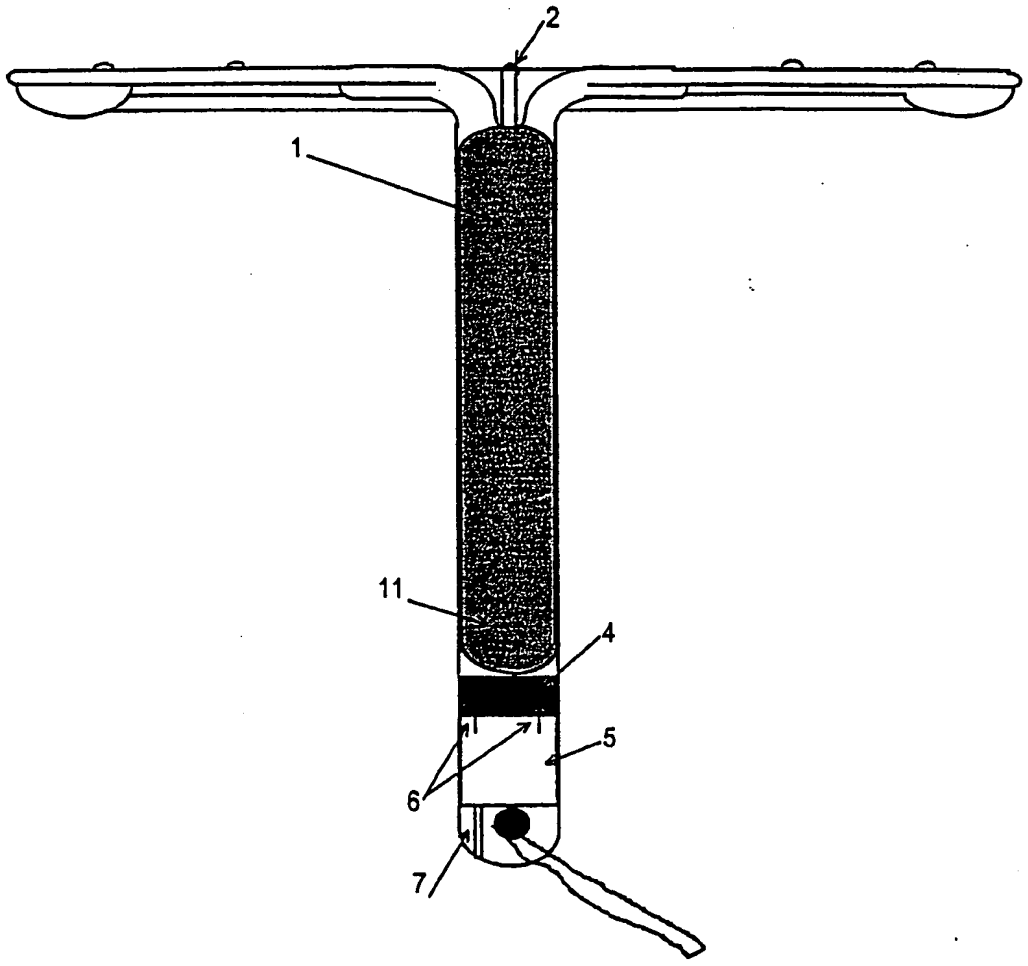


FIG 16

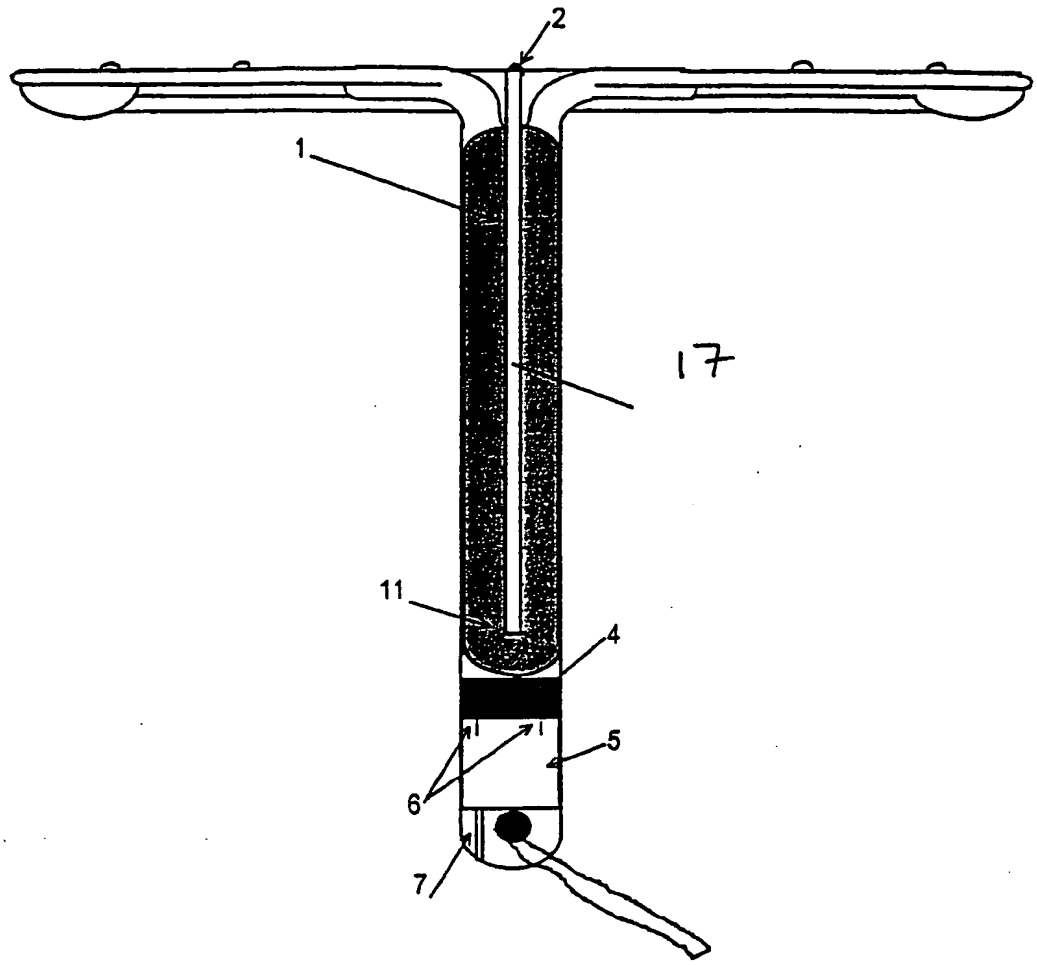


FIG 17

FIG 18A

FIG 18B

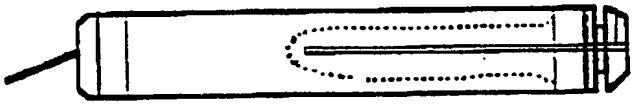


FIG 18C

FIG 18D

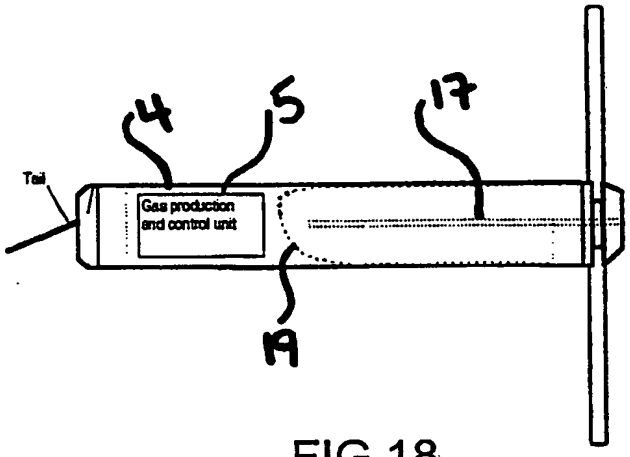
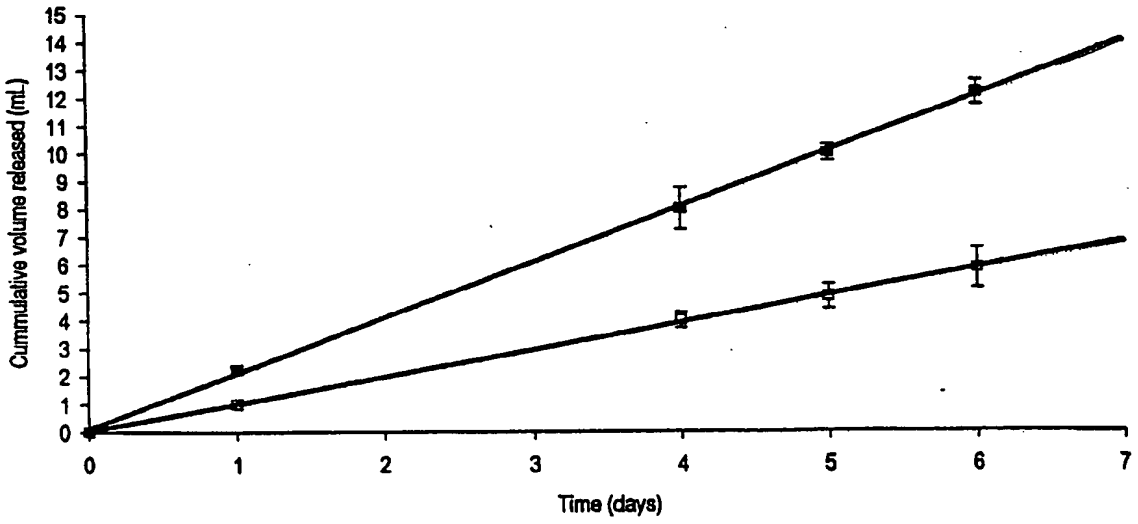


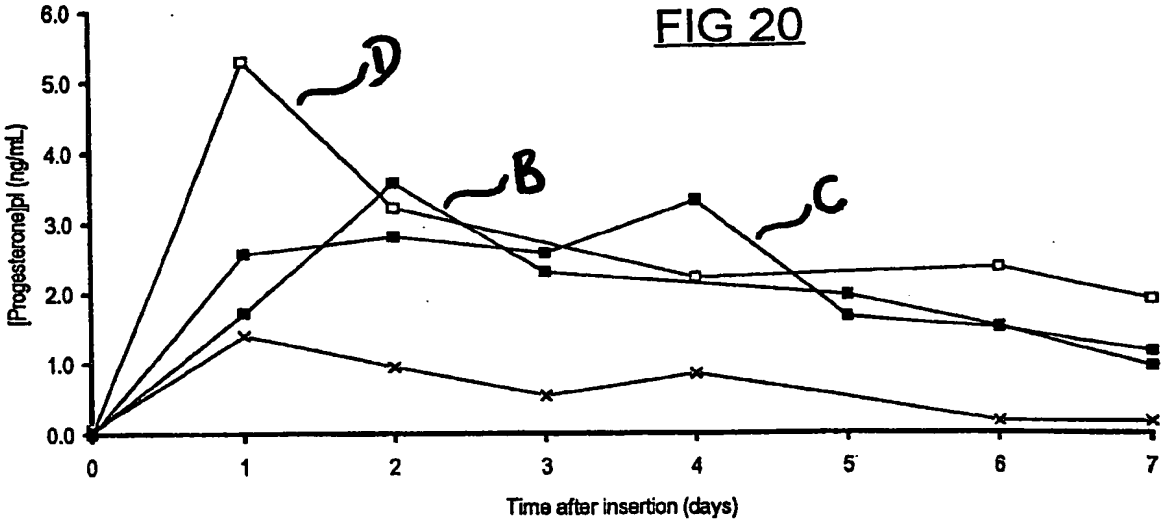
FIG 18



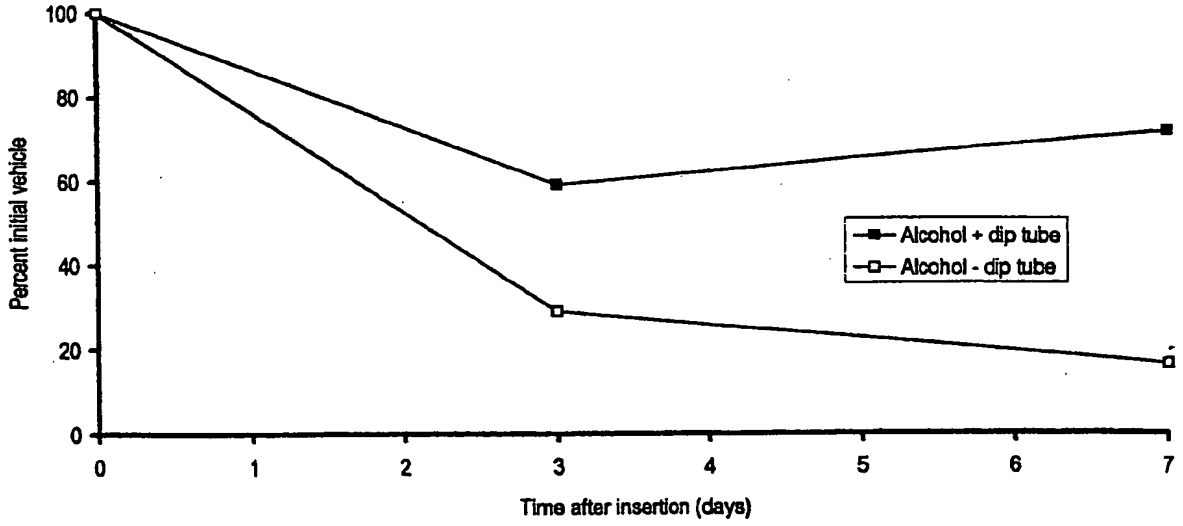
This figure shows the *in vitro* release rate of vehicle from a device using two different currents (250 mA (□) and 500 mA (■)) and therefore rates of gas production. Errorbars are standard error mean (n=3).

FIG 19

FIG 20



This figure shows the plasma progesterone levels obtained using 2 devices with a gas production and control unit (■) or one without a gas and control production unit (x). Also shown is the plasma progesterone concentration for a conventional CIDR-B (□, n=4).



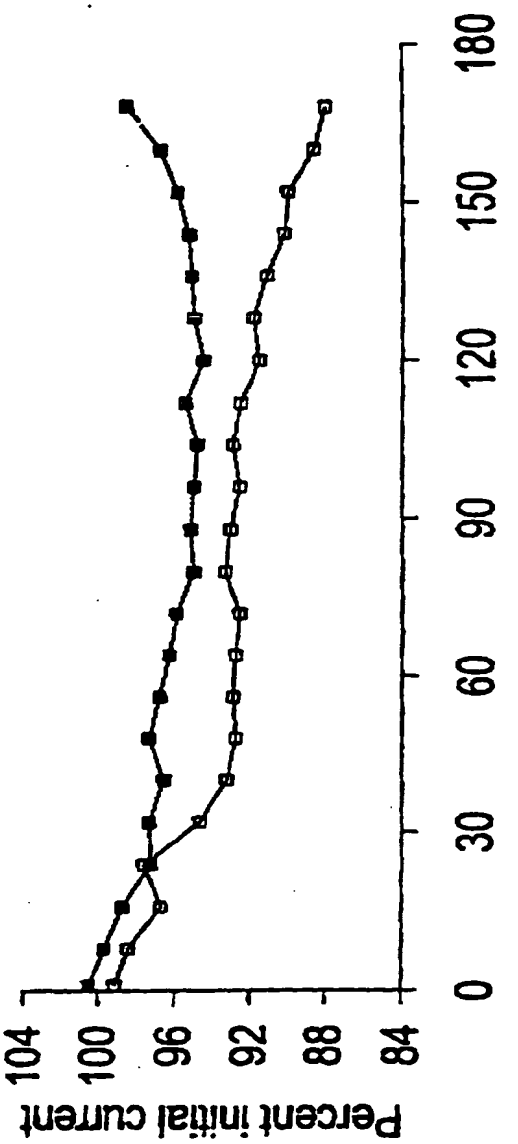
This figure shows the effect of a dip tube upon the *in vivo* retention of vehicle when there is no gas production and control unit. If no dip tube is present (□) approximately 80% of the vehicle is lost due to passively leaking from the delivery orifice, compared to only approximately 30-40% loss when a dip tube is present (■).

FIG 21

FIG 22B

FIG 22A

Figure (A) circuit diagram for the controlled production of gas by a hydrogel electrolytic cell.
Figure (B) circuit diagram for the controlled production of gas by a hydrogel electrolytic cell.



This figure shows the percent initial current as a function of time. EGel (■ n=3) and NaCl (□ n=3).

FIG 23

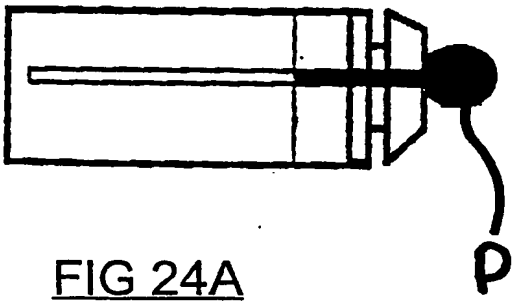


FIG 24A

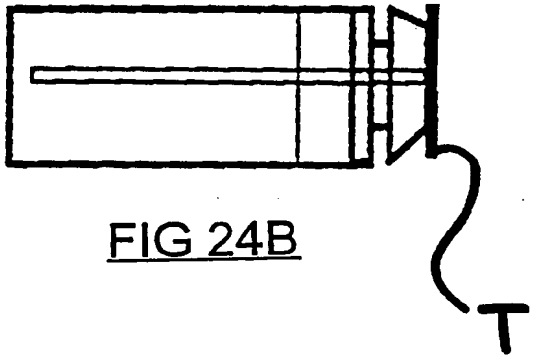


FIG 24B

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/NZ 98/00011

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61D 19/00, A61F 6/08, A61M 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61D 19/-, A61F 6/-, A61M 31/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT:- INTRA:, INTERNAL, UTERINE, UTERUS, CAVITY, VAGINA, IN VIVO, DELIVER, ADMINISTER, SUBSTANCE, DRUG, PROGESTERONE, OESTROGEN, HYDROGEL, GAS, WATER, PRESSURE, ELECTROLYSIS, ELECTRIC, CURRENT, ELECTRODE, SYNCHRONISE, OESTRUS
JAPIO:- SAME AS WPAT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2154875 A (AHI OPERATIONS LIMITED) 18 September 1985 Figures 1-7	1-3, 5-7, 10-21
Y	WO 96/29025 A1 (ADVANCED ANIMAL TECHNOLOGY LIMITED) 26 September 1996	1-3, 5-7, 10-21
Y	WO 94/01165 A1 (ELAN MEDICAL TECHNOLOGIES LIMITED) 20 January 1994	1-3, 5, 6, 10-21

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 1998	25 JUN 1998
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer STEVEN WEISS Telephone No.: (02) 6283 2466

INTERNATIONAL SEARCH REPORT

international Application No.
PCT/NZ 98/00011

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96/04953 A1 (ELAN MEDICAL TECHNOLOGIES LIMITED) 22 February 1996	1-3, 11-21
Y	US 5492534 A (ATHAYDE et al.) 20 February 1996	1-3, 5-7, 11, 13-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/NZ 98/00011

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
GB	2154875	AU	39077/85	CA	1231602	DE	3507086
		DK	942/85	FR	2560516	IT	1183767
		NL	8500578	NZ	207341	US	4678463
		ZA	8501447				
WO	9629025	AU	51274/96	EP	820258		
WO	9401165	AU	45123/93	US	5318557	WO	9401165
		EP	820258	WO	9629025	EP	651667
		NZ	253782	ZA	9304956		
WO	9604953	AU	31214/95	EP	776228	IE	940643
US	5492534	WO	9515191	US	5318540	EP	731719
		AU	62263/94				

END OF ANNEX